UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/986,632	11/09/2001	Michelle Aguera	P06974US01/BAS	5956

881 7590 10/21/2004

STITES & HARBISON PLLC
1199 NORTH FAIRFAX STREET
SUITE 900
ALEXANDRIA, VA 22314

EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicants 10/18/04 RA

Office Action Summary	Application No.	Applicant(s)	
	09/986,632	AGUERA ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,29 and 36* is/are pending in the application.

4a) Of the above claim(s) *29 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of a response filed, 07/29/2004, which includes amendments to claims 1, 6 and 11-14 and Declarations under Rule 132 by M. Belin and B. Zalc (hereinafter Belin Dec. and Zalc Dec. respectively).

All objections and rejections not repeated herein are hereby withdrawn. Where applicable a response to Applicants' arguments with respect to objections/rejections maintained will be included in the body of the objection/rejection. Claims 1-16 are pending and under consideration in this action. Claims 29 and 36 are pending but withdrawn from consideration as being drawn to non-elected subject matter. As no new grounds of rejections are set forth, **this action is made FINAL**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 6-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention**.

Applicants' assertion that the disclosure establishes that Applicants were in possession of the claimed invention is not deemed persuasive. Therefore, this rejection is maintained for reasons set forth and of record, which are repeated herein. Applicants' arguments are addressed below (infra, Response to Arguments). Base claim 6 is drawn to a method of "administering to a patient...a therapeutically effective amount..." [Emphasis added] of several compounds with the aim to prevent and treat myelin disorders. The claims read on in vivo administration of compounds of disparate character (e.g. antibodies, proteins and antisense molecules), each inhering a biologically distinct potential mode of delivery and potential effect, all with the aim of preventing or treating any myelin disorder. Put another way the claim reads on a genus of therapeutic compounds.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification does not contain any examples of administering a therapeutic agent *in vivo* to prevent or treat a myelin disorder. There is a single example *in vitro* of administering antibodies to CRMP2 and CRMP5 resulting in reduced Sema3A inhibition of axonal process extension. (Fig. 11D). Even if this single example were presented *in vivo*, it would not be sufficient to obviate a written description rejection. For example, antibodies and antisense (i.e. nucleic acid molecules) would each face different obstacles (e.g. degradation or lack of delivery

to target sites) to varying degrees. Put another way, each therapeutic agent is biologically distinct, thus one embodiment does not appear to be interchangeable with the next. Each of the therapeutic embodiments encompassed in claim 6 would inhere unique attendant characteristics that form the basis of distinction amongst proteins, antisense molecules, antibody and aptamers. Therefore, the disclosure is not descriptive of the complete structure of a representative number of species, which the claims encompass, as one of ordinary skill in the art cannot envision all therapeutically effective amounts of all the proposed agents based on the teachings in the specification. In sum it must therefore be considered that the single disclosed species is not a representative number of species sufficient to convince the skilled artisan that applicant is in possession of the claimed genus.

Response to Arguments

Applicants' arguments are in essence limited to the assertion that because modulation of CRMP may be involved in demyelination then Applicants are in possession of a sufficient number of therapeutic compounds, whether antibodies, proteins, antisense molecules or aptamers, all directed to preventing or treating myelin disorders. Applicants assert that CRMP is involved in myelination and as a target for treatment of myelin disorders, one of skill would recognize that any of the claimed embodiments would be useful for controlling expression of myelin in treating or preventing myelin disorders. (Remarks, page 3). In other words, Applicants are contending that based merely on the assertion that CRMP is a target then one of skill could envisage each of the embodied therapeutic agents, including dosage, mode of delivery and modifications necessary to alleviate adverse effects (e.g. immune response), all with the intended outcome of preventing myelin disorders outright or treating myelin disorders. First, the written

description rejection was never grounded on the fact that one of skill could not envision what compounds such as antisense molecules or antibodies can be used to modulate expression. Rather, the rejection was based on the ground that one of skill could not envision what is a therapeutic effective amount for a protein, an antibody, an antisense molecule or an aptamer. In other words, for there to be sufficient disclosure either in the art or in the instant specification, there would have to be more than a disclosure identifying what compounds can be used to modulate expression of a given protein or a family of proteins. For one of skill to conclude that Applicants were in possession of the claimed genus, there would have to be sufficient disclosure identifying for example the quantity, dosage, mode of delivery or other modifications (e.g. antisense molecule backbone modifications to ensure stability) all with the functionality of treating or preventing myelin disorders. Based on the structurally distinct nature of each of the therapeutic agents, each has an attendant biologically distinct characteristic that would affect functionality. For example, in the context of the claimed invention, merely identifying an antisense molecule as an agent that may regulate gene expression *in vivo* is not equivalent to identifying a therapeutic antisense molecule that regulates gene expression *in vivo* to a degree sufficient to prevent or treat myelin disorders.

In addition, Applicants assert that the specification describes examples of screening for modulating agents that may control myelin expression. However, identifying a compound that may affect expression *in vitro* does not necessarily equate to identification of the factors that in sum equate to a therapeutic agent. For example, assuming that the art or the specification provided information as to the amount of an antibody against a CRMP protein, the mode of delivery necessary to evade the patient's immune system, the necessary modifications (e.g.

humanizing of antibodies raise in mice) to the antibody and the mode of delivery for a particular tissue target area, then one of skill could envisage said antibody (i.e. therapeutic agent) to prevent or treat a myelin disorder. However, such hypothetically known characteristics for an antibody cannot be translated or extrapolated for an antisense or an aptamer molecule. In other words, the embodiments encompassed by the claims are not interchangeable, thus one of skill cannot not envisage each therapeutic agent.

The Belin Dec. or the Zalc Dec. do little to provide information with respect to identification of therapeutic amounts of the various embodiments. The Belin Dec. indicates that modulation of CRMP during demyelination in a murine model of Multiple Sclerosis (MS) using CRMP1 knockouts suggests involvement of CRMP in demyelination. (Belin Dec., page 3). The Zalc Dec. alleges that CRMPs are a new target for increasing myelin formation and thus remyelination. (Zalc Dec., page 2 bridging to page 3). There is nothing in the declarations to identify the necessary characteristics to envisage an antibody, aptamer or antisense molecule as a therapeutic agent to prevent or treat a myelin disorder. The declarations stand for the assertion that there may be a link between CRMP modulation and myelin disorders. Clearly, demonstrating an alleged link is not equivalent to identifying a therapeutic effective amount of an antibody or any of the other claimed therapeutic agents in preventing or treating myelin related disease. In sum, Applicants' arguments as well as the Belin and Zalc Declarations do not provide additional information sufficient for one of skill to identify a therapeutic effective amount of any of the embodiments for a protein, antibody, antisense or aptamer used in a method of preventing or treating a myelin disorder in a patient.

2. **Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**

Applicants' assertion that the disclosure fully enables the claimed invention is not deemed persuasive. Therefore, this rejection is maintained for reasons of record and as repeated herein. In addition, Applicants' arguments are addressed below (infra, Response to Arguments).

The invention is drawn to a method of both preventing and treating myelin disorders, through modulation of CRMP proteins, more specifically CRMP2 and CRMP5.
The invention requires administration to a patient a therapeutically effective amount of a broad range of compounds, including protein, antibodies and nucleic acids. The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are broad in scope and breadth. The invention is drawn to a method of preventing or treating disease (i.e. myelin disorders). In addition the claims are drawn to modulating any CRMP protein, and any activity of said protein. Moreover, the method involves administration of a disparate group of therapeutic agents, including some that read on methods of gene therapy (e.g. antisense nucleic acids and nucleic

acids encoding CRMP protein), as well as pharmacological administration of proteins and antibodies.

Nature of the invention. The invention involves one of the most complex and poorly developed areas of biology/medicine: neurobiology. In addition the invention is directed toward *in vivo* applications (i.e. treatment of neurological disorders). Furthermore, to the extent that the invention is drawn to gene therapy, the level of difficulty in implementing the invention is magnified.

State of the art. The invention is directed to a particular area of neurobiology involving oligodendrocytes, which is poorly developed. Oligodendrocytes are myelinating cells of the Central Nervous System (CNS) that ensheath axonal projections, thereby facilitating salutatory conduction. These cells appear as distinct regions in the brain and spinal cord. There is not much known about factors influencing migration and selection of axonal targets for myelination. The role of collapsing response mediator proteins in migration and selection of axonal targets is not well understood. (*See*, Ricard et al. J. Neurosci. 21(18):7203-7214, at 7203 ¶ 1 (2001); *See also*, Cohen et al. J. Neurochem. 85, 1262-78, at 1262, ¶ 1 (2003)).

Indeed the state of the art is only in the nascent stages of development, and "The fact that neurons and oligodendrocytes may respond to similar signals, mediated by Ulip/CRMPs, *opens new fields of investigation* into the role of the neuron/oligodendrocyte interaction in axonal growth..." ([Emphasis added]; *See* Ricard et al. at 7213, last ¶). The Ulip/CRMP family of proteins is expressed in developing neurons in the brain as shown in rat models. However, different Ulip/CRMP proteins are expressed differentially throughout the central nervous system (as shown in rats), suggesting that each protein may have a specific role in allowing specific

neurons to respond to particular axonal guidance. (*See* Wang and Strittmatter. J. Neurosci. 1996; 16(19): 6197-207, at 6206, col. 2). Furthermore, CRMPs are likely involved with different semaphorins and it is possible that several CRMPs mediate different intracellular actions, in selected areas of the nervous system. (*Id.*) Semaphorins are thought to act as a repellent guidance cue for a variety of axons in the developing brain (e.g. inhibiting axonal outgrowth). It would follow *a priori*, that merely modulating a given CRMP (i.e. CRMP2), which interacts with a given semaphorin (i.e. Sema3A), does not necessarily translate into prevention or treatment of myelin disorders. In sum the state of art of using CRMPs in prevention and treatment of myelin disorders is under developed.

In addition, viz., gene therapy the state of art is also poorly developed. "...there is still no conclusive evidence that gene-therapy protocol has been successful in the treatment of a human disease." (Anderson, Nature, 392: 25-30, at 25 (1998)).

Unpredictability of the art. As the state of the art is poorly developed, it would follow that there is a great deal of unpredictability as to whether modulating CRMP proteins *in vivo* would prevent or provide treatment for myelin disorders.

Moreover, with regard to the invention reading on gene therapy, there is a great deal of unpredictability. Gene therapy is still a highly unpredictable art within biology and medicine. For example, nucleic acids encoding therapeutic products may be erroneously inserted, thus disrupting a particular gene resulting in unknown, adverse or detrimental effects. (*See*, Check, E., Nature, 421: 678 (2003)) (citing occurrence of leukemia due to insertion nucleic acids used in gene therapy into a particular stretch of DNA); (*see also*, Juengst, ET. BMJ, 326:1410-11(2003)) (indicating that gene transfer often has multiple and unpredictable effects on cells).

Amount of guidance provided. Applicant's contention is that modulation *in vivo*, of expression of Ulip/CRMP proteins using several proposed agents, will result in prevention or treatment of myelin disorders. The primary justification for this conclusion is that the proteins are highly expressed in developing neurons (shown in rats) and some members of this protein family play a role in semaphorin inhibition of oligodendrocyte processes. There is actually nothing in the disclosure to indicate the myelin sheathing is necessarily enhanced or inhibited by the proposed modulation of any Ulip/CRMP protein. Put another way, the guidance provided only invites the skilled artisan to further experimentation, because the Ulip/CRMP family of proteins affect different semaphorins differentially and multiple CRMPs may interact with a specific semaphorin, for example. (*See supra*, Wang and Strittmatter, at 6206, col. 2). Therefore, it would follow that given the amount of guidance provided and the state of the art, *in vitro* results presented would not necessarily translate into implementing the invention *in vivo*. This is reasonable because even if modulation of a single CRMP protein *did* affect a particular semaphorin (e.g. thereby enhancing myelination or axonal outgrowth), it would not be reasonably true that *in vivo* modulation would result in prevention or treatment. Especially, since no *in vivo* guidance or working examples are provided.

The disclosure does provide some generic guidance as to making some of the supposed therapeutic agents (e.g. using the SELEX process to identify aptamers), however, notably, there is no guidance as to using any of the therapeutic agents (e.g. compounds in claim 6), *in vivo*, to effectuate prevention or treatment of a myelin disorder. For example, viz., gene therapy, there is no indication whether the invention can be implemented using transfection vectors or liposome formulations. Alternatively, viz., administration of purified protein, there is no indication as to

the path of delivery, dosage levels or the potential for adverse reactions. On whole, the disclosure does not provide guidance for one of ordinary skill in the art to implement the invention.

Number of working examples. The disclosure does not provide any working examples for treatment of a subject. The specification only teaches expression patterns of CRMP2 and CRMP5 in cells obtained from adult rat brain. Furthermore, the specification teaches an *in vitro* example where rat brain oligodendrocytes were examined with regard to Sema3A effects (i.e. loss of axonal outgrowth; Spec. at 35), whereby addition of anti-CRMP2 and anti-CRMP5 antibodies to the culture reduced Sema3A inhibition of axonal process extension. (Fig. 11D). This single *in vitro* example does not enable one of skill in the art to use the invention given the unpredictability of outcomes when altering gene expression *in vivo*.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of working example, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Response to Arguments

Applicants assert that the specification fully enables the claimed invention but do not further elaborate how so. As indicated in the analysis above, the instant specification is limited to *in vitro* teachings where antibodies against CRMP2 and CRMP5 reduced Sema3A inhibition of axonal process extension. Clearly, such teachings cannot be extrapolated or translated into information that would deem *in vivo* prevention and treatment of disease as routine

experimentation, for reasons outlined in the foregoing analysis (e.g. immune response, differential expression and functionality of CRMP proteins).

Applicants further assert, based on the Belin and Zalc Declarations, that there is ample disclosure in regard to making and using the claimed invention. As noted previously, the information provided in the Belin and Zalc Declarations may suggest that CRMP proteins are suitable targets in treatment. However, even is such a link is true, in and of itself such a disclosure is nothing more than an invitation to further experimentation, which in the realm of prevention and therapy of myelin disorders would certainly not be routine. In other words, identifying a target does not equate to providing adequate information to one of ordinary skill in the art to use the claimed invention without undue experimentation. The Belin Dec. uses CRMP1 knockouts in a murine model of MS to suggest CRMP involvement in demyelination. There is nothing in the disclosure to show *in vivo* administration of any therapeutic agent to prevent or treat a myelin disorder. Furthermore, the Zalc Dec. suggests that CRMPs are a target for increasing myelin formation, but there is nothing in the declaration to indicate to one of skill how to use gene regulation mechanisms *in vivo* to prevent or treat myelin disorders in humans or in mice for that matter.

In sum, Applicants arguments are predicated on the assertion that by identifying a potential target for gene regulation in and of itself is enough to provide enablement. As pointed out in the foregoing discussion this simply is not the case. Therefore, it must be deemed that the disclosure in light of what is known in the art does not provide sufficient knowledge to one of skill to make and use the claimed invention.

Conclusion

No claims are allowed. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday, from 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center at 866-217-9197 (toll-free).

Respectfully,
Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER